Benefits and risks of adjunctive inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis
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CRD summary
This review concludes that adjunctive inhaled corticosteroid (ICS) and long-acting β₂-agonist (LABA) therapy compared with long-acting bronchodilator monotherapy, is associated with a reduced risk of exacerbations, but an increased risk of pneumonia and oral candidiasis in patients with chronic obstructive pulmonary disease (COPD). Overall, despite some concerns, the findings of the review appear to be supported by the data presented.

Authors' objectives
To determine the effects of adjunctive inhaled corticosteroids (ICS) in severe or very severe chronic obstructive pulmonary disease (COPD).

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Clinical Trials were searched up to April 2008. Search terms were reported. Reference lists from relevant trials, reviews and clinical guidelines were also scanned. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) comparing mortality or exacerbation rates over a period of at least 24 weeks, in patients with COPD, receiving ICS with either long-acting β₂-agonists (LABAs) or tiotropium versus a long acting bronchodilator alone, were eligible for inclusion in the review. Eligible participants with COPD had to have a forced expiratory volume in one second (FEV₁) of less than 80% and a FEV₁/forced vital capacity ratio of less than 70%. Other eligible outcomes included the St. George's Respiratory Questionnaire (SGRQ) score, the number of study withdrawals, the incidence of pneumonia and the incidence of oral candidiasis.

The majority of included studies evaluated fluticasone (250mcg or 500mcg twice daily) and the remainder evaluated budesonide (320mcg twice daily), in combination with LABA. The mean age of included participants ranged from 63.2 to 67.7 years. Approximated 70% of included participants were male and 45% were current smokers with a mean pack-history of approximately 46 years. The majority of participants were classed as having severe COPD with a FEV₁ of between 36% and 44.6%. Study follow-up ranged from 24 to 156 weeks.

Two reviewers independently assessed studies for inclusion and discrepancies were resolved through discussion.

Assessment of study quality
Study validity was assessed using the Jadad scale and studies with a score of less than 3 points (out of a maximum of 5), were defined as poor quality. The authors do not state how the validity assessment was performed.

Data extraction
The authors do not state how data were extracted for the review or how many reviewers performed the data extraction. Exacerbations were reported as rate ratios. Mortality, withdrawals and adverse events were reported as relative risks (RRs) with 95% confidence intervals (CIs). Changes in SGRQ score were reported as mean changes (with standard error) and differences of 4 or more units were considered to indicate a clinically important improvement.

Methods of synthesis
Pooled rate ratios, RRs and weighted mean differences (WMDs) were calculated with 95% CIs. In addition the number needed to treat (NNT) or number needed to harm (NNH) were also calculated with 95% CIs. Both fixed-effect and random-effects methods were used for the analyses; however only random effects data were reported except where stated. Statistical heterogeneity was assessed using the Q statistic and $I^2$. Significant heterogeneity was indicated by $P<0.10$ and $I^2>50%$. Egger weighted regression, trim and fill methods and visual inspection of funnel plots were used to
investigate publication bias. Further analyses were carried out for the different LABAs and for trials of poor quality (Jadad score less than 3).

**Results of the review**

Nine RCTs (n=7,992) were included in the review. Three studies scored the maximum 5 points on the Jadad scale, two scored 4 points and four scored 3 points.

Statistically significant differences in the exacerbation rate (rate ratio 0.82; 95% CI: 0.72, 0.92; seven studies), SGRQ scores (WMD -1.98; 95% CI: -2.56, -1.40; six studies) and study withdrawals (RR 0.83; 95% CI: 0.74, 0.93; eight studies) were reported in favour of ICS and LABA combination therapy, in comparison with bronchodilator monotherapy. However, significant statistical heterogeneity was detected for the outcomes of exacerbation and withdrawal. No significant differences were reported in mortality rates (eight studies). Statistically significant increases in the risk of pneumonia (RR 1.68; 95% CI: 1.28, 2.21; five studies) and oral candidiasis (RR 2.93; 95% CI: 1.94, 4.42; six studies) were reported in the ICS and LABA group, in comparison with bronchodilator monotherapy. Sensitivity analyses did not significantly alter these findings. Egger weighted regression suggested that the risk of publication bias was low.

**Authors' conclusions**

ICS and LABA combination therapy compared with long-acting bronchodilator monotherapy, is associated with a reduction in the risk of exacerbations, but an increased risk of pneumonia and oral candidiasis in patients with COPD.

**CRD commentary**

This review answers a clearly defined question and searches a number of sources for relevant studies. No language restrictions were applied and tests for publication bias suggested that the risk of bias was low for most, but not all, outcomes. Some attempts were made to reduce reviewer bias and error when selecting studies, but it is unclear whether similar precautions were taken when assessing study quality and extracting data. The quality of the studies was generally good and no studies were defined as poor quality. Data were pooled using appropriate methods and heterogeneity assessed. Sensitivity analyses were conducted to assess the robustness of the data. Some differences were detected in the baseline characteristics of participants and end points used; statistical heterogeneity was detected in one of the main outcomes. However, despite some concerns about the differences between studies and the review methods, the findings of the review appear to be supported by the data presented.

**Implications of the review for practice and research**

Practice: The authors stated that, although the review does not suggest a clinically significant benefit overall for ICS in combination with LABA, this does not preclude clinically significant benefits in individual patients. When making individual treatment decisions, a reduction in exacerbations needs to be weighed against the risk of adverse events and additional costs of therapy.

Research: The authors stated that studies are required to assess the pharmacoeconomic impact of ICS and LABAs in comparison with bronchodilator monotherapy. The authors also noted the lack of studies of tiotropium versus tiotropium monotherapy.

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